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| 09/144,838 | 08/31/1998 | MICHAEL A. SIANI | GRFN-020/01U | 5261 |

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| ART UNIT | PAPER NUMBER |
| 1627 | |

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31

Please find below and/or attached an Office communication concerning this application or proceeding.

file copy

| Office Action Summary | Application No. 09/144,838 | Applicant(s) Siani et al. |
|---|---|---|
| | Examiner Bennett Celsa | Art Unit 1627 |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1) ☒ Responsive to communication(s) filed on *Apr 4, 2002* .

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

**Disposition of Claims**

4) ☒ Claim(s) *28-36* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *28-36* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

**Application Papers**

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

## DETAILED ACTION

### *Response to Amendment*

Applicant's amendment dated 4/4/02 in paper no. 30 is acknowledged.

### *Status of the Claims*

Claims 28-36 are currently pending and under consideration.

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

### *Election/Restriction*

2. Applicant's election without traverse of native chemical ligation as the elected species in Paper No. 13 is again acknowledged. Accordingly, a complete reply to the final rejection must include cancelation of nonelected subject matter or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

### *Withdrawn Objection (s) and/or Rejection (s)*

Applicant's amendment has overcome the objection to the disclosure.

Applicant's amendment has overcome the indefinite rejection found in items A, B and D in the prior office action.

Applicant's amendment to recite "head to tail" chemoselective ligation has overcome the the anticipation rejection of claims 28-31 by Canne et al., JACS Vol. 117 (1995) pages 2998-3007; the anticipation rejection of claims 28-30 by Clark-Lewis et al., J. Biol. Chem. Vol. 269 No. 23 (6/94) pages 16075-16081; and the obviousness rejection of claims 28-30 and 32-35 over

Clark-Lewis et al., J. Biol. Chem. Vol. 269 No. 23 (6/94) pages 16075-16081 and Pavia et al., Biorg. & Medicinal Chem. Lett. Vol. 3, No. 3 pages 387-396.

The 102b/103 rejection of claims 28-31 over the Canne et al. and Dawson reference has been rewritten in order to address applicant's amended claims (e.g.defining N and C terminus and addressing head to tail ligation).

**Outstanding Objection(s) and/or Rejection (s)**

3. Claims 33 and 34 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention (NEW MATTER REJECTION).

Amending claims 33 and 34 to change the libraries to encompass N-terminal peptide and C-terminal peptide segments derived from different **families** of parent proteins instead of different parent proteins constitutes new matter; e.g. neither supported in the specification nor does applicant indicate where such support is present. Applicant must cancel the new matter in response to this rejection.

***Discussion***

Applicant's arguments directed to the above new matter rejection were considered but deemed nonpersuasive for the following reasons.

Applicant argues that original claims 32, 35 and specification page 8, lines 9-12 when read together provide support for ligating different classes of proteins. Applicant's argument was considered but deemed nonpersuasive for the following reasons.

Claim 32 claims the ligation of fragments derived from two different PARENT proteins; whereas claim 35 address a preferred embodiment wherein the parent proteins are from the same CLASS. Applicant's argument that the specification supports the claiming of DIFFERENT protein classes is not persuasive since the specification provides no direct support for ligating DIFFERENT classes of proteins nor is there a single example addressing the ligation of different class proteins. Applicant's logic that the OPPOSITE of the preferred embodiment found in oritiginal claim 35 must be supported is clearly faulty. For example, generic claim 32 may comprise two different parent proteins such as insulin and an insulin analog/derivative or may comprise parent proteins from the same class such as oxtocin/vasopressin (e.g. peptide hormones of analogous function); and NOT encompass different protein families such as *peptide antibodies* and peptide *hormones*.

Accordingly, the above new matter rejection is hereby retained.

4. Claims 28-36 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention (INADEQUATE WRITTEN DESCRIPTION REJECTION).

The specification fails to provide sufficient written description to support a genus of cross-over proteins which are devoid of sequence length, amino acid content, specific biological function which is produced by the presently claimed method of ligating one or more peptide segments derived from one or more first protein(s) and one or more second protein(s) whether of the same or different family or classes. There is a limited showing of ligating protein fragments from the same "class" of protein (e.g. chemokines: such as RANTES etc.) but no examples regarding the ligation of peptide fragments from different classes. Different classes of compounds would lack a common core structure which elicits a common activity and would broadly encompass both functionally and structurally distinct peptides including hormones, enzymes etc.

In this regard, applicant is referred to the seminal case of *University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and the resulting "Guidelines for Examination of Patent Applications Under the 35 USC 112, first paragraph, 'Written Description' Requirement" published in 1242 OG 168-178 (January 30, 2001).

It is first noted that written description is legally distinct from enablement: "Although the two concepts of are entwined, they are distinct and each is evaluated under separate legal criteria. The written description requirement, a question of fact, ensures the that the inventor conveys to others that he or she had possession of the claimed invention; whereas, the enablement requirement, a question of law, ensures that the inventor conveys to others how to make and use the claimed invention." See 1242 OG 169 (January 30, 2001) citing *University of California v. Eli Lilly & Co*

With regard to the description requirement, Applicants' attention is directed to The Court of Appeals for the Federal Circuit which held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1405 (1997), quoting *Fiers v. Revel,* 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original)[The claims at issue in *University of California v. Eli Lilly* defined the invention by function of the claimed DNA (encoding insulin)].

However, it is clear that applicant has not presented an adequate sample to demonstrate possession of the presently claimed invention. See *University of California v. Eli Lilly and Co.* U.S. Court of Appeals Federal Circuit ( CA FC) 43 USPQ2d 1398 7/22/1997 Decided July 22, 1997 No. 96-1175 regarding adequate disclosure, the analysis of which does not address the absence or presence of undue experimentation.

For the specification discloses only limited examples that are neither representative of the claimed genus (which is not limited by peptide length or amino acid composition nor types of derivations), nor is it clear that they represent a substantial portion of the claimed genus. This showing clearly does not provide an adequate representation regarding the myriad possible cross-over proteins or peptides of different length which lack a common core which would be expected to elicit a common activity.

***Discussion***

Applicant's arguments directed to the above written description rejection were considered but deemed nonpersuasive for the following reasons.

Applicant attempts to distinguish the "Lilly" decision as addressing a composition whereas the present invention is directed to a method of *forming* a molecule (a "cross-over protein"). This argument is not persuasive.

Applicant's method of making clearly requires that applicant have possession of the reactants. Accordingly, if applicant lacks possession of the different classes of proteins as reactants; applicant's **use** of these protein classes in a method of making similarly lacks written description. Thus, a finding of a lack of written description for cDNA mammalian insulin nucleotides in "Lilly"; would necessitate a similar finding by the "Lilly"court of lack of written description of a claim addressing the (assay/diagnostic) use of the same cDNA's for detecting diabetes by use of the nucleotides **as a probe**. This is consistent with the Written Description Guidelines which are NOT limited to compound or composition claims. Additionally, applicant's argument is inconsistent with the Supreme Court which held that in order for a method to be enabled (or useful), merely being able to reproduce the method steps is insufficient where the final product is not useful.. Eg. See *Brenner v. Manson*, 383 U.S. 519, 148 USPQ 689 (1966). Accordingly, enablement (or utility) issues drawn to compound (e.g. a product) is indeed germaine to the enablement of a process of making a compound (e.g a product).

Applicant next argues that "no caselaw holds that an Applicant must set forth every possible combination and permutation of amino acid residues for such segments in order to obtain a claim reciting the word protein". Applicant's argument is misguided.

The caselaw (Lilly , its progeny and the Guidelines) requires that the present applicant provide sufficient support to demonstrate possession of a claimed invention drawn to the use of different "classes" or proteins. The above rejection provides unrebutted arguments and rationalae, consistent with caselaw and the Guidelines, as to why the original specification and original claims fails to provide sufficient written description to demonstrate possession of the claimed amended scope.

Accordingly, the above rejection is hereby retained.

5. Claims 28-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

C. In claims 30, 33-35 (and claims dependent thereon) the terms "same (different) *family* of protein molecules" are relative terms which renders the claims indefinite. The term "family of protein molecules" is not defined by the claim, nor does the specification provide a standard for ascertaining the requisite degree of relatedness (structure, function , conformation etc.) of various proteins to be classifiable as being from the same or different families, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Additionally, neither the

specification nor claims indicate what characteristics (e.g. chemical, structure, conformational etc) distinguishes one "family" of proteins from another.

***Discussion***

Applicant's arguments directed to the above indefinite rejection were considered but deemed nonpersuasive for the following reasons.

In response to the above indefinite rejection applicant's argue that "the term 'family of proteins' is a term of art that would be readily understood by those of ordinary skill in the art." In support applicant cites "multiple databases of protein families" and provides lists of patents in which "[T]he term 'protein family' is ... used in the specification and claims".

Applicant's argument is deficient since it fails to address the crux of the above indefinite rejection e.g. that the terms "same (different) *family* of protein molecules" are relative terms which are not defined by the claim, nor does the specification provide a standard for ascertaining the requisite degree of relatedness (structure, function , conformation etc.) of various proteins to be classifiable as being from the same or different families, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Additionally, neither the specification nor claims indicate what characteristics (e.g. chemical, structure, conformational etc) distinguishes one "family" of proteins from another. The mere use of the term by others does not render the term definite as used in the present context. Nor does applicant indicate what the "term of art" definition is in the present context (or as used in the cited databases or patent for

that matter) so as to apprise one of ordinary skill what would infringe or not infringe the present claims..

Accordingly, the above indefinite rejection is hereby maintained.

6. Claims 28-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Canne et al., JACS Vol. 117 (1995) pages 2998-3007, Dawson et al. Science Vol. 266 (11/94) pages 776-779 and Pavia eta l., Biorg. & Medicinal Chem. Lett. Vol. 3, No. 3 pages 387-396.

Canne et al. disclose a chemical ligation chemoselective method of making both **hetero-** and homo- **dimers** utilizing a "***modular strategy***" (abstract) (emphasis provided). The Canne et al. method extends the native peptide ligation (e.g. see page 2999, beginning of left paragraph and citation no. 13 to Science article: herein the "Science article") chemoselective technique to other ligation chemistries (e.g. thioesters, oximes, hydrazones, disulfides, thiazolidones etc.: see page 2999 left column) and to the formation of "complex protein analogues" (not just single protein syntheses as described in the Science article) which would allow for the condensation or more than two (e.g. "Three or more") unprotected **peptide segments** in a specific manner utilizing chemical ligation (emphasis provided). Accordingly, the Canne et al. Reference suggests the use of chemoselective chemical ligation to condense two or more peptide segments one or in a multiple manner using the native chemical ligation strategy (e.g. in the Science article) and/or different chemoselective ligation chemistries. The Canne reference further teaches the use of chemoselective chemical ligation (e.g. including native chemical ligation) in a modular strategy to

generate heterodimers utilizing two or more fragments of transcriptional regulatory proteins (e.g. cMyc and Max) that comprise protein domains (e.g. see schemes and figures especially schemes 1 and 3). Accordingly, the Canne et al. Reference method discloses the use of reactants (e.g. peptide segments derived from different proteins which comprise different functional domains e.g. "functional protein module(s)") which are chemoselectively ligated to form "cross over proteins" within the scope of the presently claimed inventions. It is noted that the Canne et al. reference explicitly teaches the ligation of peptide fragments which contain "reactive groups" (e.g. derived carboxyl terminus) that form "cross over proteins".

With respect to the presently claimed invention (as amended) which encompasses head to tail ligation (amino terminal amino acid of a fragment to to carboxyl terminal of a different fragment) to form a cross over protein; it is noted that the Canne et al. reference specifically recites the application of a small number of types of chemical ligation techniques which preferably include the Science article native chemical ligation approach (e.g. see Science article page 777 Fig. 1) which illustrates head-to-tail covalent ligation.

Accordingly, the Canne reference incorporation of the Science reference article describing the native chemical ligation approach (e.g. head to tail ligation) would render its selection from such a limited number of ligation techniques either immediately envisages (e.g anticipation) or alternatively obvious to one of ordinary skill in the art at the time of applicant's invention. E.g. See *In re Schaumann*, 572 F.2d 312. 197 USPQ 5 (CCPA 1978). As further taught by the Canne reference, "This study demonstrates that a *molecular approach*, wherein *independent*

*functional or structural units are joined by chemical ligations*, is a feasible method of protein syntheses. This technique can construct proteins of unusual structure with full biological activity, thus providing a powerful new way to study important biological phenomena. The **chemical ligation** approach to the total chemical synthesis of proteins has the potential to take protein syntheses far beyond the the realm of nature. Mutually compatible ligation chemistries, such as the thioester- and oxime-forming reactions reported here, can be used for the ligation of a number of different unprotected peptide segments in a convergent manner". See page 3004 up to "Experimental Section".

From the above, citation and the reference article taken as a whole, it is clear that the Canne et al. reference teaches the extension of the Dawson "chemical ligation" approach to incorporate "independent functional or structural units by chemoselective ligation".

Additionally, the Canne et al. Reference teaching taken alone, or in conjunction with the teaching of the Science reference, teaches the making of prospective analogues (e.g. ligands) by chemical ligation of peptide fragments one at a time for biological evaluation.

To the extent that the Canne et al. refernece alone or in combination with the Dawson referencfe differs from the presently claimed invention (e.g. claims 32-36) which is drawn to the making and screening of libraries of ligands for biological evaluation; the Pavia et al. Reference is offered.

The Pavia et al. reference teaches that the traditional serial process of synthesizing and testing peptide analogues one at a time is being replaced by the use of combinatorial library

syntheses strategies since the libraries provide the ability to increase molecular diversity and utilize high throughput screening which optimizes drug discovery See e.g. Pavia et al. Abstract; page 391 ("Automated Methods").

Accordingly, one of ordinary skill in the art would be motivated to generate libraries of compounds by utilization of the Canne reference modular strategy in order to optimize drug discovery.

Thus, modification of the Canne reference method alone or in view of the Science reference ligation technique to utilize combinatorial libraries would have been obvious to one of ordinary skill in the art at the time of applicant's invention in order to optimize drug discovery.

***Discussion***

Applicant's arguments addressing the above obviousness rejection over the Canne, Dawson and Pavia references were considered but deemed nonpersuasive for the following reasons. Initially, it is noted that the above rejection was modified in response to applicant's amendment.

Applicant argues that the Dawson et al. reference teaches the use of native chemical ligation to synthesize a "non-crossover' protein. Additionally, applicant argues that the Pavia reference "provides no more than a general review of combinatorial chemistry methods unrelated to those of the present invention."

In response to applicant's arguments against the Dawson et al. or Pavia references individually, one cannot show nonobviousness by attacking references individually where the

rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant further argues that the Canne et al. reference teaches C-terminal to C-terminal ligation of two peptide domains.

This argument is not persuasive since it fails to appreciate the teaching of the Canne et al. article taken as a whole to one of ordinary skill in the art. In this regard, Canne et al. specifically cites the Dawson et al. Reference chemical ligation head-to-tail technique which was introduced by the SAME authors and the general applicability of this tecnique to all different types of ligation chemistries and peptides (see page 2999, left column) and to the formation of "complex protein analogues" (not just single protein syntheses as described in the Science article) which would allow for the condensation or more than two (e.g. "Three or more") unprotected **peptide segments** in a specific manner utilizing chemical ligation (emphasis provided).

Applicant further argues that the Dawson and Canne et al. articles cannot be combined to suggest the present invention since "The citation of the Dawson et al. reference in the Canne et. al. Reference is intended to show the use of an alternative, not a conjunctive, chemical syntheses approach, citing page 299 of Canne et al. in support: "The syntheses of functional protein analogues containing unnatural backbone elements represents an important conceptual breakthrough that demonstrates that we need not be restricted to the formation of native peptide bonds in order to have biologically active protein."

Applicant's arguments were considered but not deemed persuasive for the following reasons.

Initially, the cited Canne et al. passage appears to teach one of ordinary skill in the art to apply the syntheses of functional protein analogues to the Dawson head to tail chemical ligation strategy.

Additionally, Applicant's argument is misguided since it fails to appreciate the Canne et al. reference teaching as a whole as illustrated by the following passage which places applicant's quoted citation in its full perspective:

"This study demonstrates that a *molecular approach*, wherein *independent functional or structural units are joined by chemical ligations*, is a feasible method of protein syntheses. This technique can construct proteins of unusual structure with full biological activity, thus providing a powerful new way to study important biological phenomena. The **chemical ligation** approach to the total chemical synthesis of proteins (e.g. Dawson's method) has the potential to take protein syntheses far beyond the the realm of nature. Mutually compatible ligation chemistries, such as the thioester- and oxime-forming reactions reported here, can be used for the ligation of a number of different unprotected peptide segments in a convergent manner". See page 3004 up to "Experimental Section".

From the above citation, and the reference article taken as a whole, it is clear that the Canne reference teaches the extension of the Dawson "chemical ligation" approach to incorporate "independent functional or structural units by chemoselective ligation.

Accordingly, the above obviousness rejection is hereby maintained.

***Double Patenting***

7. Claims 28-31 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims (e.g. claims 1-7) of U.S. Patent No. 6,184,344 in view of Canne et al., JACS Vol. 117 (1995) pages 2998-3007.

The Patent claims teach native chemical ligation approach (e.g. head to tail ligation) of a first and second oligopeptide.

The patent claims fail to teach the use of oligopeptide fragments from different proteins (e.g. comprising a functional protein module) to form a cross-over (e.g hybrid) proteins .

However, the Canne et al. Reference disclose a chemical ligation chemoselective method of making both **hetero-** and homo- **dimers** utilizing a "***modular strategy***" (abstract) (emphasis provided). The Canne et al. method extends the native peptide ligation (e.g. see page 2999, beginning of left paragraph and citation no. 13 to Science article: herein the "Science article") (which is synonymous with the patented claim method) chemoselective technique to other ligation chemistries (e.g. thioesters, oximes, hydrazones, disulfides, thiazolidones etc.: see page 2999 left column) and to the formation of "complex protein analogues" (not just single protein syntheses as described in the Science article) which would allow for the condensation or more than two (e.g. "Three or more") unprotected **peptide segments** in a specific manner utilizing chemical ligation (emphasis provided). Accordingly, the Canne et al. Reference suggests the use of chemoselective chemical ligation to condense two or more peptide segments once or in a multiple manner using

the native chemical ligation strategy (e.g. in the Science article) and/or different chemoselective ligation chemistries.

Accordingly, the Canne reference teaching of the use of chemoselective chemical ligation (e.g. including native chemical ligation) in a modular strategy to generate heterodimers utilizing two or more fragments of transcriptional regulatory proteins (e.g. cMyc and Max) that comprise protein domains (e.g. see schemes and figures especially schemes 1 and 3) would motivate one of ordinary skill in the art to utilize the patented claim process in the Canne modular strategy and thus render obvious the presently claimed invention..

8. Claims 32-36 are rejected under 35 U.S.C. 103(a) as being rejected for obviousness-type double patenting over U.S. Patent No. 6,184,344 in view of Canne et al., JACS Vol. 117 (1995) pages 2998-3007 as applied to claims 28-31 above, and further in view of Pavia et al., Biorg. & Medicinal Chem. Lett. Vol. 3, No. 3 pages 387-396.

The '344 and Canne et al. combined teaching of making prospective analogues (e.g. ligands) by chemical ligation of peptide fragments one at a time for biological evaluation differs from the presently claimed invention (e.g. claims 32-36) which is drawn to the making and screening of libraries of ligands for biological evaluation.

However, the Pavia et al. reference teaches that the traditional serial process of synthesizing and testing peptide analogues one at a time is being replaced by the use of combinatorial library syntheses strategies since the libraries provide the ability to increase

molecular diversity and utilize high throughput screening which optimizes drug discovery See e.g. Pavia et al. Abstract; page 391 ("Automated Methods").

Accordingly, one of ordinary skill in the art would be motivated to generate libraries of compounds by utilization of the '344 and Canne et al. reference method in order to optimize drug discovery.

Thus, modification of the '344 and Canne et al. reference method technique to utilize combinatorial libraries would have been obvious to one of ordinary skill in the art at the time of applicant's invention in order to optimize drug discovery.

9. Claims 28-31 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims (e.g. claims 1-7) of U.S. Patent No. 6,326,468 in view of Canne et al., JACS Vol. 117 (1995) pages 2998-3007.

The Patent claims teach native chemical ligation approach (e.g. head to tail ligation) of a first and second oligopeptide.

The patent claims fail to teach the use of oligopeptide fragments from different proteins (e.g. comprising a functional protein module) to form a cross-over (e.g hybrid) protein .

However, the Canne et al. Reference disclose a chemical ligation chemoselective method of making both **hetero-** and homo- **dimers** utilizing a "***modular strategy***" (abstract) (emphasis provided). The Canne et al. method extends the native peptide ligation (e.g. see page 2999, beginning of left paragraph and citation no. 13 to Science article: herein the "Science article") (which is synonymous with the patented claim method) chemoselective technique to other ligation

chemistries (e.g. thioesters, oximes, hydrazones, disulfides, thiazolidones etc.: see page 2999 left column) and to the formation of "complex protein analogues" (not just single protein syntheses as described in the Science article) which would allow for the condensation or more than two (e.g. "Three or more") unprotected **peptide segments** in a specific manner utilizing chemical ligation (emphasis provided). Accordingly, the Canne et al. Reference suggests the use of chemoselective chemical ligation to condense two or more peptide segments one or in a multiple manner using the native chemical ligation strategy (e.g. in the Science article) and/or different chemoselective ligation chemistries.

Accordingly, the Canne reference teaching of the use of chemoselective chemical ligation (e.g. including native chemical ligation) in a modular strategy to generate heterodimers utilizing two or more fragments of transcriptional regulatory proteins (e.g. cMyc and Max) that comprise protein domains (e.g. see schemes and figures especially schemes 1 and 3) would motivate one of ordinary skill in the art to utilize the patented claim process in the Canne modular strategy and thus render obvious the presently claimed invention..

10. Claims 32-36 are rejected under 35 U.S.C. 103(a) as being rejected for obviousness-type double patenting over U.S. Patent No 6,326,468 in view of Canne et al., JACS Vol. 117 (1995) pages 2998-3007 as applied to claims 28-31 above, and further in view of Pavia et al., Biorg. & Medicinal Chem. Lett. Vol. 3, No. 3 pages 387-396.

The '468 and Canne et al. combined teaching of making prospective analogues (e.g. ligands) by chemical ligation of peptide fragments one at a time for biological evaluation differs from the presently claimed invention (e.g. claims 32-36) which is drawn to the making and screening of libraries of ligands for biological evaluation.

However, the Pavia et al. reference teaches that the traditional serial process of synthesizing and testing peptide analogues one at a time is being replaced by the use of combinatorial library syntheses strategies since the libraries provide the ability to increase molecular diversity and utilize high throughput screening which optimizes drug discovery See e.g. Pavia et al. Abstract; page 391 ("Automated Methods").

Accordingly, one of ordinary skill in the art would be motivated to generate libraries of compounds by utilization of the '468 and Canne et al. reference method in order to optimize drug discovery.

Thus, modification of the '468 and Canne et al. reference method technique to utilize combinatorial libraries would have been obvious to one of ordinary skill in the art at the time of applicant's invention in order to optimize drug discovery.

***Discussion***

The above double patenting rejections are retained. Applicant states that a terminal disclaimer will be filed upon the indication of allowable subject matter.

*New Objection (s) and/or Rejection (s)*

11. Claims 28-31 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Canne et al., JACS Vol. 117 (1995) pages 2998-3007 and Dawson et al. Science Vol. 266 (11/94) pages 776-779 cited in the Canne et al. Reference at page 6588 footnote (13) to demonstrate the inherent teaching of head-to-tail ligation of "the chemical ligation approach to the total chemical syntheses of proteins". See MPEP 2131.01 which permits the citation of an additional reference (in this case an incorporated reference) to either "explain the meaning of a term used in the primary reference" and/or "inherency" e.g. that the Dawson chemical ligation is head to tail ligation.

Canne et al. disclose a chemical ligation chemoselective method of making both **hetero-** and homo- **dimers** utilizing a "***modular strategy***" (abstract) (emphasis provided). The Canne et al. method extends the native peptide ligation (e.g. see page 2999, beginning of left paragraph and citation no. 13 to Science article: herein the "Science article") chemoselective technique to other ligation chemistries (e.g. thioesters, oximes, hydrazones, disulfides, thiazolidones etc.: see page 2999 left column) and to the formation of "complex protein analogues" (not just single protein syntheses as described in the Science article) which would allow for the condensation or more than two (e.g. "Three or more") unprotected **peptide segments** in a specific manner utilizing chemical ligation (emphasis provided). Accordingly, the Canne et al. Reference suggests the use of chemoselective chemical ligation to condense two or more peptide segments once or in a multiple manner using the native chemical ligation strategy (e.g. in the Science article) and/or

different chemoselective ligation chemistries. As further taught by the Canne reference, "This study demonstrates that a *molecular approach*, wherein *independent functional or structural units are joined by chemical ligations*, is a feasible method of protein syntheses. This technique can construct proteins of unusual structure with full biological activity, thus providing a powerful new way to study important biological phenomena. The **chemical ligation** approach to the total chemical synthesis of proteins has the potential to take protein syntheses far beyond the the realm of nature (emphasis provided). Mutually compatible ligation chemistries, such as the thioester- and oxime-forming reactions reported here, can be used for the ligation of a number of different unprotected peptide segments in a convergent manner". See page 3004 up to "Experimental Section".

From the above, citation and the reference article taken as a whole, it is clear that the Canne et al. reference teaches the extension of the Dawson "chemical ligation" approach to incorporate "independent functional or structural units by chemoselective ligation".

Additionally, the Canne et al. Reference teaching taken alone, or in conjunction with the teaching of the Science reference, teaches the making of prospective analogues (e.g. ligands) by chemical ligation of peptide fragments one at a time for biological evaluation.

The Canne reference further teaches the use of chemoselective chemical ligation (e.g. including native chemical ligation) in a modular strategy to generate heterodimers utilizing two or more fragments of transcriptional regulatory proteins (e.g. cMyc and Max) that comprise protein domains (e.g. see schemes and figures especially schemes 1 and 3). Accordingly, the Canne et al.

Reference method discloses the use of reactants (e.g. peptide segments derived from different proteins which comprise different functional domains e.g. "functional protein module(s)") which are chemoselectively ligated to form "cross over proteins". It is noted that the Canne reference explicitly teaches the ligation of peptide fragments which contain "reactive groups" (e.g. derived carboxyl terminus) that form "cross over proteins".

Thus, the Canne reference incorporation of the Science reference article describing the native chemical ligation approach (e.g. head to tail ligation) would render its selection from such a limited number of ligation techniques either immediately envisaged (e.g anticipated) or alternatively obvious to one of ordinary skill in the art at the time of applicant's invention. E.g. See *In re Schaumann*, 572 F.2d 312. 197 USPQ 5 (CCPA 1978).

***Information Disclosure Statement***

Applicant requested Examiner consideration of references not previously considered by the Examiner. Applicant is requested to provide a new 1449 listing references which were submitted, but not previously considered by the Examiner.

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

**General information regarding further correspondence**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Celsa whose telephone number is (703) 305-7556.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jyothsna Venkat (art unit 1627), can be reached at (703)308-0570.

Any inquiry of a general nature, or relating to the status of this application, should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Bennett Celsa (art unit 1627)

June 14, 2002

BENNETT CELSA
PRIMARY EXAMINER